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TITLE: Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet, and Breast Cancer

PRINCIPAL INVESTIGATOR: Maureen Sanderson, Ph.D.

CONTRACTING ORGANIZATION: University of South Carolina
Columbia, South Carolina 29208

REPORT DATE: June 2003

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13. ABSTRACT (Maximum 200 Words)

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance will be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity will modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

During the third year of the study, Dr. Sanderson helped develop a course in Nutritional Epidemiology, conducted analyses of dietary intake, anthropometric measurements and insulin-like growth factor I from the Shanghai Breast Cancer Study, submitted a proposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer, and participated in the Lower Rio Grande Valley Nutrition Intervention Research Initiative consortium.

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Table of Contents

Introduction

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance would be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity would modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

Body

I submitted a new proposal to transfer this Career Development Award from the University of South Carolina to the University of Texas School of Public Health at Brownsville on July 12, 2001. To my knowledge, this transfer is still pending. At the suggestion of my first annual report review, I sent a revised Statement of Work on August 21, 2001 (Appendix A). As a result of my relocation some of the tasks that were planned for months 1-24 will be completed during months 25-48.

During the first year of the study, I completed Task 1.a. by auditing Pathology of Neoplasia with Dr. Kim Creek at the University of South Carolina School of Medicine in Fall 2000. I partially completed Task 1.c. by gaining knowledge of analyses of dietary intake and anthropometric measurements; I co-authored the manuscript "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India" and presented the poster "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population" at the Society for Epidemiologic Research Meeting in June 2001. I partially completed Task 1.e. by submitting an Idea Award to the Department of Defense entitled "Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer" in June 2000.

During the second year of the study, the manuscripts on oral precancerous lesions and breast cancer were published. I partially completed Task 1.c. by being added as a co-investigator to the Texas School Physical Activity and Nutrition (SPAN) survey, a statewide assessment of nutritional status and physical activity of elementary, middle and high school students. I partially completed Task 1.e. by submitting a preproposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer with investigators from the University of Texas at Brownsville (UTB, Dr. Gerson Peltz, PI) and from the University of Texas School of Public Health (UTSPH, Dr. Maureen Sanderson, PI). I completed Task 2.a. by auditing Introduction to Genetic and Molecular Epidemiology with Drs. Xigeng Wu, Debbie del Junco and Corinne Aragaki at the University of Texas School of Public Health in Spring 2002. I partially completed Task 2.c. by presenting the poster on "Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Society for Epidemiologic Research Meeting in June 2002.

During the third year of the study, I completed Task 1.b. by assisting Dr. R. Sue Day (formally McPherson) develop a course on Nutritional Epidemiology that I will co-teach in Spring 2004 (Appendix B). I partially completed Task 1.c. by conducting analyses of dietary intake and anthropometric measurements of Behavioral Risk Factor Surveillance System data conducted on the Texas-Mexico border (Appendix C). I partially completed Task 1.d. by working with Dr. Day and other members of the Lower Rio Grande Valley Nutrition Intervention Research Initiative (LRGVNIRI) consortium conducting analyses for a monograph on nutrition research and services in the LRGV (Appendix D). I completed Task 1.e. by submitting a full proposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer (Appendix E). The proposal was funded and has a start date of September 1, 2003. I completed Task 2.c. by conducting an oral presentation on "Soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Department of Defense Era of Hope Breast Cancer Research Program Meeting in September 2002, and by submitting a manuscript on this topic (Appendix F). I also completed Task 2.c. by publishing a letter entitled "Reply 1: An assessment of the preconceptional mitochondrial hypothesis" (Appendix G).

During the fourth year of the study, I will complete Task 1.c. by conducting analyses of biochemical indicators and breast cancer from a New Mexico study that Dr. Day participated in as a co-investigator. I will complete Task 1.d. by working with the LRGVNIRI to validate a food frequency questionnaire for use with this population. I will complete Task 2.b. by attending the Harvard University summer course in genetic epidemiology taught by Dr. Melissa Austin. I will complete Tasks 2.c. and 2.d. by collecting information and beginning to investigate dietary intake, estrogen, insulin-like growth factor-I, insulin, glucose and breast cancer risk using the newly DOD-funded South Texas Women's Health Project. I will complete Task 2.e. by working with the LRGVNIRI consortium to submit a grant to follow a cohort of children from birth through age 12 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity.

Key Research Accomplishments

- Completed Task 1.b. by assisting Dr. R. Sue Day (formally McPherson) develop a course on Nutritional Epidemiology that I will co-teach in Spring 2004.

- Partially completed Task 1.c. by conducting analyses of dietary intake and anthropometric measurements of Behavioral Risk Factor Surveillance System data conducted on the Texas-Mexico border.

- Partially completed Task 1.d. by working with Dr. Day and other members of the Lower Rio Grande Valley Nutrition Intervention Research Initiative (LRGVNIRI) consortium conducting analyses for a monograph on nutrition research and services in the Lower Rio Grande Valley.

- Completed Task 1.e. by submitting a full proposal for a HBCU/MI Partnership Award to the Department of Defense to investigate insulin resistance and breast cancer.

- Completed Task 2.c. by conducting an oral presentation on "Soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Department of Defense Era of Hope Breast

Cancer Research Program Meeting in September 2002, and by submitting a manuscript on this topic.

- Completed Task 2.c. by publishing a letter entitled "Reply 1: An assessment of the preconceptional mitochondrial hypothesis."

Reportable Outcomes

1) Manuscripts

Sanderson M, Shu XO, Zheng W. Reply 1: An assessment of the preconceptional mitochondrial hypothesis. Br J Cancer 2003;88:1819-1820.

Sanderson M, Shu XO, Jin F, Yu H, Dai Q, Malin A, Gao Y-T, Zheng W. Insulin-like growth factor-I, soyfood intake and breast cancer risk. Cancer Epidemiol Biomarkers Prev (submitted May 2003).

2) Abstracts

Sanderson M, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Soyfood intake, insulin-like growth factor-I and breast cancer risk. DOD Era of Hope Breast Cancer Research Program Meeting Proceedings P35-31.

3) Grants

Name:	Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women
Funding Agency:	U.S. Army Medical Research and Materiel Command
Period of Funding:	September 1, 2003 – August 31, 2007
Role:	Principal Investigator of UTSPH subcontract (10% effort years 1-5, 0% support years 1-2)

Conclusions

To date, my breast cancer research has focused on surrogate markers of intrauterine exposure to estrogen and subsequent breast cancer. This research has led me to the understanding that prenatal and postnatal growth represent critical periods in breast carcinogenesis, in large part due to exposure to estrogen and other hormones/growth factors. Clearly, dietary intake is associated with prenatal and postnatal growth. Diet also has been related to estrogen, insulin-like growth factor-I (IGFI) and other hormones/growth factors, and to breast cancer. Elevated levels of IGFI and insulin, and abdominal obesity are markers for insulin resistance, which has been positively associated with breast cancer in several studies.

This Career Development Award will investigate an area of recent interest in breast cancer, the interrelationships of prenatal and postnatal growth, hormones, diet, and breast cancer. The possibility that insulin resistance may tie these factors together has led to my goal of

studying the association between insulin resistance and breast cancer. A secondary goal is to assess the influence of genetic susceptibility, diet and physical activity on this association.

The Lower Rio Grande Valley (LRGV) of Texas is an exceptional location to perform breast cancer research because 85 percent of the population is Hispanic. Hispanic women in the LRGV have a relatively low incidence of breast cancer compared with non-Hispanic white women. In comparison with Hispanic women in the US, Hispanic women residing in the LRGV have a higher mortality from breast cancer. In contrast, Hispanic women are at greater risk of insulin resistance. This research will allow us to investigate whether the reduced risk of breast cancer among Hispanic women in the LRGV may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity.

In summary, the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among certain ethnic groups in the US. Should insulin resistance prove to be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

References

Sanderson M, Shu X-O, Jin F, Dai Q, Wen W-Q, Hui Y, Gao Y-T, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Int J Cancer 2001;92:899-905.

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Am J Epidemiol 2001;153:75.

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao Y-T, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-88.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr 2002;5:303-312.

Sanderson M, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk. Am J Epidemiol 2002;155:75.

Sanderson M, Shu XO, Zheng W. Reply 1: An assessment of the preconceptional mitochondrial hypothesis. Br J Cancer 2003;88:1819-1820.

Appendices

Appendix A

Statement of Work

Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

Task 1. Undergo intensive training in cancer biology and nutritional epidemiology, and conduct case-control studies of the insulin resistance-breast cancer relationship, Months 1-24:

a. Audit course in the pathology of neoplasia taught by Dr. Kim Creek
b. Audit course in nutritional epidemiology taught by Dr. R. Sue McPherson
c. In collaboration with Dr. R. Sue McPherson, assess nutritional status and physical activity, and conduct nutritional analyses of dietary intake, biochemical indicators and anthropometric measurements using her ongoing studies at the University of Texas School of Public Health at Houston
d. In collaboration with Dr. R. Sue McPherson, conduct analyses and prepare a manuscript for a validation study of a food frequency questionnaire used in her ongoing studies at the University of Texas School of Public Health at Houston
e. In collaboration with senior colleagues, submit grants to investigate the association between insulin resistance and breast cancer using an ongoing case-control study, the Shanghai Breast Cancer Study (R01-CA64277, PI Zheng) of 1500 cases and 1500 controls

Task 2. Undergo intensive training in molecular and genetic epidemiology, and conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels, Months 25-48:

a. Audit course in molecular epidemiology taught by Dr. Corinne Aragaki
b. Attend the Harvard University summer course in genetic epidemiology taught by Dr. Melissa Austin
c. In collaboration with Dr. Xiao Ou Shu, conduct analyses and prepare a manuscript investigating whether adolescent/adult diet and physical activity modifies the effect of estrogen and insulin-like growth factor 1 (IGF1) on breast cancer using a recently funded ancillary study from the Shanghai Breast Cancer Study
d. In collaboration with Dr. Wei Zheng, conduct analyses and prepare a manuscript investigating whether genetic susceptibility and adolescent/adult diet and physical activity modify the effect of estrogen, IGF1, insulin and C-peptide on breast cancer among women in Shanghai
e. In collaboration with senior colleagues, submit a grant to conduct a cohort study of 800 mothers and their female infants to investigate the association between maternal age, diet, preeclampsia, and infant birth weight, and hormone levels using the infants' cord blood; children will be followed for 12 years and childhood/adolescent weight, height, diet and physical activity will be assessed at 4-year intervals

Appendix B

PH2998: Section: 100
NUTRITIONAL EPIDEMIOLOGY
Drs. R. Sue Day and Maureen Sanderson

COURSE DESCRIPTION

PREREQUISITES: (Introduction to Epidemiology and Biometry, or equivalent) Students need to have knowledge of epidemiologic study designs, be able to understand correlations, regression analyses and other statistical measures of agreement, basic nutrition and ability or willingness to learn a statistical software program.

LOCATION AND TIME: Wednesday, Room W-608, 1-4 p.m.

INSTRUCTORS:

R. Sue Day, Ph.D.
Office: W-916
Telephone: 500-9317
FAX: 500-9329
E-Mail: rena.s.day@uth.tmc.edu
Message center: W-914
Office hours by appointment

Maureen Sanderson, Ph.D.
Office: 2.202 A Brownsville
Telephone: 956-554-5162
FAX: 956-554-5152
E-Mail: msanderson@utb.edu

Office hours by appointment

OBJECTIVES:

The objective of the course is to describe and evaluate the issues associated with nutritional assessment of populations using food and nutrient, biochemical and anthropometric data. A combined lecture, seminar and hands-on approach is taken to examine the strengths and weaknesses of the various nutritional assessment methodologies for use with each of the major epidemiological study designs. Epidemiological studies of the relationship of nutrition and chronic diseases are critically evaluated. Students will be given a data set and guided opportunities to explore methodologies of statistical analysis and interpretation of nutritional data as part of the learning experience. Reading material include textbooks and selections from the current literature.

The objectives for the course are:

1. To describe the issues associated with nutritional assessment of populations.
2. To determine the strengths and weaknesses of the various nutritional assessment methodologies for use with the major epidemiologic study designs.
3. To describe the issues associated with utilization of nutrient data base systems.

4. To calculate the number of food records and sample size requirements for nutritional assessments using a nutritional data set.

5. To calculate validity and reliability measurers for a nutritional data set.

6. To compute energy adjusted nutrients using a nutritional data set.

7. To identify potential confounding factors associated with the measurement of food and nutrient intake and its association with disease.

8. To design a nutritional assessment of a given population to address a research question in an epidemiologic study.

9. To evaluate the design and methods used in the nutritional epidemiologic literature.

ASSESSING COMPETENCY:

As with all classes at the School of Public Health the only grades registered will be Pass, Fail, Withdrew, and Incomplete. Comments on student performance will be forwarded to evaluation committees.

To receive a "Pass", a student must:

(1) attend and participate in class,
(2) complete reading assignments,
(3) complete all homework/class assignments with a grade of 70 or greater, and
(4) complete both mid-term and final exams with a grade of 70 or greater.

If a student needs to miss class for any reason, contact the instructor prior to the class or leave a message as soon as possible. Assignments turned in after the 'due date' class will be considered late and points will be deducted from the total. If a student has an arranged absence cleared with the instructor, an acceptable turn in date should be negotiated when the absence is discussed. No assignment will be accepted more than I week late.

Students may withdraw from the course at any time before the final grade is released. An "Incomplete" will be registered only when serious illness or similar unavoidable circumstances have prevented completion of the term project or other assignments.

TEXTBOOKS:

Walter Willett. Nutritional Epidemiology, 2nd edition. Oxford University Press 1998.

Barrie M. Margetts and Michael Nelson (eds). Design Concepts in Nutritional Epidemiology, 2nd edition. Oxford University Press 1997.

Other texts which are available in the library and contain relevant material are:

Rosalind S. Gibson. Principles of Nutritional Assessment. Oxford University Press 1990.

Rosalind S. Gibson. Nutritional Assessment. A laboratory manual. Oxford University Press 1993.

Derrick B. Jelliffe and E. F. Patrice Jelliffe. Community Nutritional Assessment. Oxford University Press 1989.

Nutrient Adequacy: Assessment Using Food Consumption Surveys. National Academy Press 1986.

Smith, J.L. (ed) Nutrient databank directory, 9 Edition, University of Delaware, 1993

Mason, J.B. et al. Nutritional surveillance, WHO, Geneva, 1984

Mayrent, S.L. (ed) (Hennekens) Epidemiology in Medicine, Little, Brown and Company, 1987

Abramson, J.H. Survey Methods in Community Medicine, 4 Edition, Churchill Livingston, 1990

Himes, J.H. (ed) Anthropometric Assessment of Nutritional Status, Wiley-Liss, 1991

Whitehead, R.G. (ed) New Techniques in Nutritional Research Vol.9, Academic Press, 1991

FAQ Conducting Small-scale Nutrition Surveys. A Field Manual. Nutrition in Agriculture #5, 1990

Anderson, S.A. (ed) Guidelines for Use of Dietary Intake Data. Prepared for the Center for Food Safety and Applied Nutrition, FDA, Dept. HHS by Life sciences research office, FASEB, December 1986

Various authors, Dietary Assessment Methods, AJCN, Volume 59, number i(s), 1994

Leaverton, P.E. A Review of Biostatistics. A program for self-instruction, 3 edition, Little, Brown, & Company, 1986

Readings will be available in class or the library for specified topics.

PH2998: NUTRITIONAL EPIDEMIOLOGY
SPRING SEMESTER 2004
DRS. R. S. DAY AND M. SANDERSON

READING LIST

Topic	Book Readings	Articles
1. Introduction	None	
2. Overview	Willett ch. 1,2,10 Margetts ch. 1,7	None
3. Holiday		
4. Causality	Hennekens p. 39-50	
5. Diet assessment	Margetts ch. 5	Anderson 1982 Beaton 1986
6. Portion sizes	Willett p. 79-83	Guthrie 1984 Samet 1984 Faggiano 1992 Clapp 1991
Data Base	Willett p. 28-32, 56-57 Margetts ch. 4	None
7. Food records/ recalls	Margetts ch. 6 Willett ch. 4	McPherson 1990
8-10. Variation & sample size	Willett ch. 3 Margetts p. 57-62	Liu 1978 Nelson 1989 Wassertheil-Smoller 1993 Miller 1991 Beaton 1979 Anderson 1986
11-12. Train/lab	None	
13. Biochemical Assessment	Margetts ch. 7	None
Stunting, Wasting, And Obesity		None
14. No class	None	
15. Diet history	Willett ch.7 Margetts ch. 6	Reed 1954 Burke 1957 Friedenreich 1992 Mann 1962

Topic	Book Readings	Articles	
16. FFQ	Willett ch. 5,6	Longnecker 1993 Briefel 1992 Rimm 1992	Block 1994 Sempos 1992 Baghurst 1992
17-18. Train/No class	None		
19. Multicollinearity	Margetts ch.3	Anderson 1986	
Adjusted Kcal Intake	Willett ch. 11	Shekelle 1987 Brown 1994	Willett 1986
20. Validity	Willett ch. 6 Margetts ch.8	Pietinen 1988 Feunekes 1993 Block 1989 Sobell 1989 Thompson 1993	Crawford 1994 van Horn 1993 Block 1990 Treiber 1990
21-22. Reliability	Willett ch. 6 Margetts ch. 8	See articles from validity	
23. Lab	None		
24. Sources of error	Margetts ch. 3 Willett ch. 12	Anderson 1986 (repeat)	
25. Associations	Hennekens ch. 4 Margetts ch. 9	None	
26. Epi. Study designs	Margetts ch. 10-13 Willett ch. 16	Anderson 1986	
27-30. Presentations	None		

PH2998: NUTRITIONAL EPIDEMIOLOGY
SPRING SEMESTER 2004
DRS. R. S. DAY AND M. SANDERSON

CLASS SCHEDULE

CLASS	DAY	DATE	TOPIC
1	MON	Jan 5	Introduction
2	WED	Jan 7	Overview of nutrition epidemiology Diet, biochemical and anthropometric assessment
3	MON	Jan 12	Holiday
4	WED	Jan 14	Causality Explanation of term project
5	MON	Jan 19	Dietary assessment of populations
6	WED	Jan 21	Issues concerning portion sizes Food composition tables and nutrient data bases
7	MON	Jan 26	Food records and 24 hour recalls
8	WED	Jan 28	Food records and 24 hour recalls
9	MON	Feb 2	Variation in intake Homework 1 Assigned: Calculation of appropriate number of food records Sample size issues associated with dietary intake Homework 2 Assigned: Calculation of sample sizes
10	WED	Feb 4	Discussion of homework Homework 1 due
11	MON	Feb 9	Explanation of keeping food records Classroom coding of food records with FIAS Homework 2 Assigned: Complete food records
12	WED	Feb 11	COMPUTER LABORATORY Coding food records with FIAS
13	MON	Feb 16	Biochemical assessment Clinical assessment of population – stunting, Wasting, and obesity

CLASS	DAY	DATE	TOPIC
14	WED	Feb 18	No class – coding of food records
15	MON	Feb 23	Diet history Food frequency questionnaires (part 1) Homework 2 due Research Question Due – Term Project
16	WED	Feb 25	Food frequency questionnaires (part 2)
17	MON	March 1	Train FFQ Interviews Homework 3 Assigned: FFQ Interviews
18	WED	March 3	No Class – FFQ Interviews
19	MON	March 8	Multicollinearity, Energy adjusted intake Homework 3 Due Homework 4 Assigned: Energy adjustment Discuss presentation date for Term Project
20	WED	March 10	Issues of validity
21	MON	March 15	Issues of validity and reliability Homework 4 Due
22	WED	March 17	Issues of reliability
23	MON	March 22	COMPUTER LABORATORY Homework 5 Assigned: Descriptive analysis and Analysis of reliability and validity data
24	WED	March 24	Sources of error: sampling error and information bias Homework 6 Assigned: Sample size
25	MON	March 29	Measures of association in epidemiologic studies And epidemiologic study designs Homework 5 Due
26	WED	March 31	Epidemiologic study designs Presentations Homework 6 Due
27	MON	April 5	Presentations

CLASS	DAY	DATE	TOPIC
28	WED	April 7	Presentations
29	MON	April 12	Presentations Term Project Due
30	WED	April 14	Presentations Course evaluation

Appendix C

A Comparison of Risk Behaviors among Texas Border and Non-border Residents. *M. Sanderson, M.E. Fernandez, R.J. Dutton, A. Ponder, D. Sosa. (University of Texas-Houston School of Public Health at Brownsville, Brownsville, TX, 78520)

Purpose: To assess whether risk behaviors differ among residents of seven border counties that comprise 95% of the 15-county border population, and 239 non-border counties in Texas.
Methods: In 2001, the Texas Department of Health's Office of Border Health conducted a Behavioral Risk Factor Surveillance System (BRFSS) telephone survey in seven border counties. This survey of health practices and risk factors supplements the statewide BRFSS. A total of 2,521 adults (ages 18-99 years) were interviewed reflecting a population of 1.3 million adults residing in those counties. For comparison, we used the 2001 Texas BRFSS which consists of 5,348 adults reflecting 13.6 million persons residing in non-border counties. Analyses were performed in SUDAAN to account for the complex survey design.
Results: Based on self-report of height and weight, 68% of border residents were overweight compared with 61% of non-border residents. This higher prevalence of overweight is driven by the difference in percentages among females (62% border vs. 54% non-border) since the male percentages are similar (71% border vs. 69% non-border). Only 7% of border residents compared to 24% (2000) of non-border residents reported they consumed 5 servings of fruits and vegetables the day prior to the interview. The percentage of border residents engaging in more than 20 minutes of physical activity most days of the week was very small (13%) compared with non-border residents (36%). The one behavioral risk factor that was not as prevalent among border (19%) as among non-border (23%) residents was current smoking. Similar percentages of border and non-border residents reported they had 60 or more alcoholic drinks in the past 30 days (6%), but a greater percentage of border (21%) than non-border (15%) residents drank five or more alcoholic drinks on an occasion in the past 30 days. This binge drinking is almost entirely among male border residents (36%) than among female border residents (7%). Among non-border residents, the disparity between male (24%) and female (7%) binge drinking is not as great.
Conclusions: The fact that many of the behavioral risk factors described above are more prevalent among border residents than non-border residents may at least partially explain why border residents suffer disproportionately from several health problems. Additional studies are needed to 1) adequately assess behaviors that put border residents at higher risk for disease; 2) examine the psychosocial and environmental factors that influence these behaviors; and 3) develop and evaluate interventions that address both behavioral and environmental risk factors related to priority health problems.

Appendix D

Lower Rio Grande Valley Nutrition Intervention Research Initiative (LRGVNIRI)
Monograph Outline

Foreword **(Margaret Bogle/Chuck Onstad)**

Executive Summary and Recommendations **(Editor)**

Chapter 1. History and Overview of the LRGVNIRI **(Margaret Bogle/Chuck Onstad)**

- Introduction
- History of the LRGVNIRI
- Overview of the Initiative
- Evolution and Organization of the Monograph
- Future of the Initiative
- Resources
- Description of each partner on Memorandum of Understanding

Chapter 2. Cultural, Demographic, Educational, Economic and Agricultural Characteristics **(Ann Millard, Nelda Mier)**

- Cultural Characteristics **(Ann Millard, Nelda Mier)**
- Demographic Characteristics **(Ann Millard, Nelda Mier)**
- Educational Characteristics **(Beth Allen - UTH has data on CDrom)**
- Economical Characteristics **(Bertha Garza, John Robinson-Ext)**
- Agricultural Characteristics **(Jose Amador, Ann Millard, Nelda Mier)**
- Summary **(Ann Millard)**
- References

Chapter 3. Health Professions and Services **(Maureen Sanderson, Shelton Brown-UTB)**

- Introduction
- Health Care Professions
- Health Care Services
- Medicaid and Medicare
- Summary
- References

Chapter 4. Nutrition Related Health Concerns

- Introduction
- Major Nutrition Related Health Concerns

1. Diabetes **(Esperanza Briones)**
    - Definition
    - Nutrition Role
    - Summary
    - References
1. Overweight/Obesity/Hypertension **(Susie Day)**
    - Definition
    - Nutrition Role
    - Summary
    - References
2. Osteoporosis **(Farzad Deyhim)**
    - Definition
    - Nutrition Role
    - Summary
    - References
3. Immunity- **(Gerson Peltz, Farzad Deyhim)**
    - Definition
    - Nutrition Role
    - Summary
    - References
4. Anemia **(Sharon Robinson)**
    - Definition
    - Nutrition Role
    - Summary
    - References
5. Cardiovascular Disease **(Esperanza Briones, Elena Bastida)**
    - Definition
    - Nutrition Role
    - Summary
    - References
6. Under-Nutrition – Food Insecurity **(Sharon Robinson)**
    - Definition
    - Nutrition Role
    - Summary
    - References
7. Cancer **(Maureen Sanderson, Gerson Peltz)**
    - Definition
    - Nutrition Role
    - Summary
    - References

8. Birth Outcomes **(Sharon Robinson/Jenna Anding)**
   - Neural Tube Defect (NTD)
     - Definition
     - Nutrition Role
     - Summary
     - References
   - Low Birth Weight (LBW)
     - Definition
     - Nutrition Role
     - Summary
     - References
   - Alcohol/Drug Addiction
     - Definition
     - Nutrition Role
     - Summary
     - Reference

Chapter 5. Food and Nutrition Programs and Resources **(Investigative Team - Julie Garza, Dahlia Lovera, Susie Day, Norma Perez, Maureen Sanderson)**

- Introduction
- Health Concern #1
  - Federal
  - Cooperative Extension
  - State Health Department
  - Local Health Department
  - Private Sector
- Health Concern #2...
  - Federal
  - Cooperative Extension
  - State Health Department
  - Local Health Department
  - Private Sector
- Summary
- References

Chapter 6. Food, Nutrition, and Health Knowledge, Attitudes, and Practices **(Maureen Sanderson, Nelda Mier)**

- Introduction
- Cultural Aspects **(Ann Millard, Nelda Mier)**
- Data on Knowledge and Attitudes Regarding Nutrition and Health
  - YRBS **(Maureen Sanderson)**
  - BRFSS **(Health Dept – 2002 Cameron, Starr, Hidalgo, 2001 Willacy) (Maureen Sanderson, Shelton Brown)**

- SPAN **(Regional data-weight monitoring - Susie Day, ? Hoelscher)**
- Summary **(Maureen Sanderson, Nelda Mier)**
- References

Chapter 7. Food and Nutrient Intake **(Bob Faraji, Esperanza Briones, Farzad Deyhim)**

- Introduction
- Food and Nutrient Intake **(Susie Day has folate data)**
  - Regional and Cultural Dietary Intake Patterns **(Bob Faraji)**
  - Data Specific to the Lower Rio Grande Valley **(Bob Faraji)**
  - CSFII **(Bob Faraji)** - will require analysis
  - NHANES **(Bob Faraji)** - will require analysis
- Supplement Use/Alternative Medicines **(Bill McIntyre, Elena Bastida has some data)**
- Summary **(Bob Faraji)**
- References

Appendix **(Investigative Team - Julie Garza, Dahlia Lovera, Susie Day, Norma Perez, Maureen Sanderson)**

- Listing of Agencies and Programs with program information from survey indexed by health concerns, county, funding sources, and alphabetically.

Appendix E

Title/Referral Page

No Page Limit

a. Proposal title (up to 160 characters)

INTERRELATIONSHIPS OF HORMONES, DIET, BODY SIZE AND BREAST CANCER AMONG HISPANIC WOMEN

b. Proposal log number

BC022338

c. PI's full name (first, middle initial, last)

GERSON PELTZ

d. Award mechanism

HBCU/MI PARTNERSHIP TRAINING AWARD

e. Keyword descriptive technical terms

ESTROGEN, PHYTOESTROGEN CONSUMPTION, ABDOMINAL OBESITY, INSULIN RESISTANCE

f. Conflicts of interest: Include the following information (no page limit)

Name	Institutional Affiliation(s)	Role(s) on Proposed Project or Perceived Conflicts of Interest
Gerson Peltz, MD	**University of Texas at Brownsville**	**Principal Investigator**
Nancy McGowan, PhD	**University of Texas at Brownsville**	**Co-Investigator**
Matthew Johnson, PhD	**University of Texas at Brownsville**	**Co-Investigator**

Name	Institutional Affiliation(s)	Role(s) on Proposed Project or Perceived Conflicts of Interest
Maureen Sanderson, PhD	**University of Texas-Houston School Public Health at Brownsville**	**Co-Principal Investigator**
Sally Vernon, PhD	**University of Texas-Houston School Public Health**	**Co-Investigator**
R. Sue Day, PhD	**University of Texas-Houston School Public Health**	**Co-Investigator**
Guillermo Tortolero-Luna, PhD	**University of Texas-Houston School Public Health at Brownsville**	**Co-Investigator**
Maria Fernandez, PhD	**University of Texas-Houston School Public Health**	**Co-Investigator**
Adriana Perez, PhD	**University of Texas-Houston School Public Health at Brownsville**	**Co-Investigator**

Log # BC022338

Principal Investigator: Peltz, Gerson

Principal Investigator: Peltz (*Last Name*) Gerson (*First Name*) *MI*

Proposal Title: Interrelationships of hormones, diet, body size and breast cancer among Hispanic women

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HBCU/MI Partnership Training Award Proposal
Table of Contents

Complete and submit with your proposal immediately after the Table of Contents to confirm that all components are included in your application.

Checklist for FY02 BCRP Program Announcement I Proposal Submission

Yes	No	
☒	☐	Proposal Information completed
☒	☐	Title/Referral Page
☒	☐	Table of Contents
☒	☐	Checklist for FY02 BCRP Proposal Submission
☒	☐	Technical Abstract (1-page limit)
☒	☐	Lay Abstract (1-page limit)
☒	☐	Statement of Work (2-page limit)
☒	☐	Proposal Relevance Statement (1-page limit)
☐	☒	Center Synergy Statement (1-page limit) (for Center)
☒	☐	Proposal Body **(adhere to page limits for the individual mechanism)**
☒	☐	Abbreviations (1-page limit)
☒	☐	References (no page limit)
☒	☐	Biographical Sketches (3-page limit per individual)
☒	☐	Principal Investigator
☒	☐	Participating investigators at HBCU/MI and collaborating institution (for HBCU/MI Partnership)
☐	☒	Collaborating investigators and other key personnel
☒	☐	Existing/Pending Support (no page limit)
☒	☐	Facilities /Equipment Description (no page limit)
		Administrative Documentation:
☒	☐	List of items included in this section
☒	☐	Letters of support from collaborating individuals and/or organizations
☒	☐	Letters of institutional commitment (2) (for HBCU/MI Partnership)
☐	☒	Documentation of IND application/exemption (for Biotechnology Clinical Partnership)
☐	☒	Intellectual property agreement (for Biotechnology Clinical Partnership)
☒	☐	Detailed Cost Estimate (no page limit)
☒	☐	Total cost estimate matches Proposal Information, item 4
☒	☐	Instruments (no page limit)
☒	☐	List of documents included in Instruments Section
☒	☐	Publications and/or Patent Abstracts (5-document limit)

NOTE: Exceeding page limits may result in proposal rejection prior to peer review. Submit only materials specifically requested or required in this program announcement. Submission of additional materials may be construed as an attempt to gain an unfair advantage.

Technical Abstract

Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

Background: The overall goal of this proposed HBCU/MI Partnership Training Award is to further strengthen the collaborative relationship between the minority institution, University of Texas at Brownsville (UTB), and the collaborating institution, University of Texas-Houston School of Public Health (UTSPH). The UTSPH established a regional campus on the UTB campus in 2001, and the Co-Principal Investigator of the partnership from UTSPH is located in Brownsville. The vision of UTB and the UTSPH Brownsville regional campus is to conduct community-based participatory research in areas deemed important by the community.

Objective/Hypothesis: The proposed training program will focus on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer among Hispanic women. We hypothesize that the clinic-based case-control study conducted as part of the training program will be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

Specific Aims: Specific aims of the proposed training program are: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, cancer epidemiology, intervention mapping, field epidemiology, biostatistics, and nutrition epidemiology offered by UTSPH faculty in-person from Brownsville and via ITV from Houston, 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw, 3) to disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics, and 4) to submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley.

Study Design: The collaborative arrangement for the HBCU/MI Partnership Training Award will consist of three UTB faculty with no history of breast cancer funding, and six UTSPH faculty with funding histories in breast and others cancers. This proposal is envisioned as occurring in two phases the Training Phase and the Investigation Phase. UTB faculty will undergo intensive training provided by UTSPH faculty during year 1. Additional training will take place in subsequent years. To reinforce training, faculty from UTB and UTSPH will conduct a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 and 3. Under the guidance of UTSPH faculty, UTB faculty will submit grants for additional funding using the breast cancer study as preliminary data in year 4.

Relevance: While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

Lay Abstract

Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

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Statement of Work

HBCU/MI Partnership Training Award

Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

Phase 1: Training phase (Year 1)

- Complete coursework toward Master's of Public Health degree
- Liaise with local medical providers, health clinics and state health agencies to encourage reporting of breast cancer to the Texas Cancer Registry
- Identify sites for data collection with local health providers and health clinics
- After consultation with local health providers design a case-control study to include completion of a questionnaire, anthropometry and a blood draw
- Develop a questionnaire appropriate for use with the local Hispanic population
- Design protocols for data collection, laboratory work, tracking system, data entry programs, and write manual of operations
- Initiate institutional review board approval through local and federal channels
- Pilot test study methods and revise the study design as needed

Phase 2: Investigation Phase (Years 2 through 4)

- Identify and recruit 500 breast cancer cases and 500 controls identified by mammography centers
- Complete questionnaires to obtain information on breast cancer risk factors, personal health history (e.g., type 2 diabetes), medication history (e.g., estrogen and insulin), and diet
- Collect anthropometric measurements and pre-diagnostic blood
- Abstract medical records for relevant health history and pathology data
- Process and store blood samples
- Complete radioimmunoassays for insulin, estrone, estradiol, and sex hormone-binding globulin, immunoradiometric assays for insulin-like growth factor-I, and insulin-like growth factor binding protein 3, and measure glucose using the glucose oxidase method
- Complete data entry of all questionnaires and assays
- Perform interim statistical analyses at end of year 2 to assess data quality
- Perform final statistical analyses to test study hypotheses
- Consult with local health providers and health clinics regarding the cancer reporting mechanism and provide training as needed
- Expand data collection to cancers other than breast cancer as a means of developing a regional Lower Rio Grande Valley cancer registry.
- Disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics
- Prepare manuscripts to report study results
- Archive dataset for future analyses and future patient follow-up
- Submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley

Proposal Relevance Statement

The overall goal of this proposed HBCU/MI Partnership Training Award is to further strengthen the collaborative relationship between the minority institution, University of Texas at Brownsville (UTB), and the collaborating institution, University of Texas-Houston School of Public Health (UTSPH). The proposed training program will focus on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer.

While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

Although cancer is a reportable condition in Texas few of the providers that diagnose cancer report cases to the Texas Cancer Registry in a timely fashion. This problem is especially apparent in the Lower Rio Grande Valley (LRGV) because the nearest regional cancer registry is located four hours away in San Antonio. Staff from the Texas Cancer Registry do not conduct active surveillance of medical records and pathology reports in the LRGV, thus the registry relies on a passive system of reporting by providers. Having undergone training in field epidemiology and case ascertainment, UTB faculty will work closely with providers to encourage an active system of reporting as a means of developing a regional cancer registry for the LRGV.

Since reporting of cancer to the Texas Cancer Registry is incomplete we plan to conduct a clinic-based rather than population-based case-control study of breast cancer as part of the training program. The establishment of a regional cancer registry for the LRGV will resolve the ascertainment of cases for population-based studies of breast cancer. While most areas of the US have over 90% telephone coverage, fewer than 72% of LRGV residents have telephones. The training UTB faculty received in control ascertainment will be instrumental in developing a system of random digit dialing combined with home interviewing for cancer studies.

We hypothesize that the clinic-based case-control study conducted as part of the training program will be useful in identifying factors associated with decreased breast cancer risk among Hispanic women. The PI from UTB and Co-PI from UTSPH have mutual interests in studying reasons why Hispanic women possess a number of breast cancer risk factors and yet have a fairly low incidence of the disease. Very few breast cancer studies have focused on Hispanic women; however, the identification of protective factors against breast cancer may contribute to our understanding of the biological mechanisms of the disease.

Data from the clinic-based case-control study will be used to submit proposals to conduct larger population-based case-control studies of breast cancer in the LRGV. UTB faculty who have undergone training can then work with other colleagues to encourage and mentor future breast cancer researchers at the university. UTSPH faculty in Brownsville will continue to work with UTB faculty to establish an outstanding breast cancer research program in the area.

Proposal Body

1. Background

The overall goal of this proposed HBCU/MI Partnership Training Award is to further strengthen the collaborative relationship between the minority institution, University of Texas at Brownsville (UTB), and the collaborating institution, University of Texas-Houston School of Public Health (UTSPH). The UTSPH established a regional campus on the UTB campus in 2001, and the Co-Principal Investigator (Co-PI) of the partnership from UTSPH is located in Brownsville. The vision of UTB and the UTSPH Brownsville regional campus is to conduct community-based participatory research in areas deemed important by the community. While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to develop an outstanding breast cancer research program in this area.

1.1. Training Program Development

The proposed training program will focus on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer among Hispanic women. The Principal Investigator (PI) from UTB has an interest in the effect phytoestrogen consumption and body fat content have on sex steroid hormone levels and subsequent breast cancer risk. The Co-PI from UTSPH is currently funded to investigate insulin resistance and breast cancer.

Cameron County, the site of the proposed research, is located at the southern tip of Texas on the Mexico border and is 84 percent Hispanic (1). The prevalence of self-reported diabetes in the LRGV (9%) is very high compared with Texas (6.2%) (2). Insulin resistance, like type 2 diabetes, is a condition characterized by high levels of insulin and by abdominal obesity (3). Insulin resistance is thought to be associated with breast cancer, and may help explain the elevated risk of breast cancer among certain ethnic groups (4). Despite being at greater risk of insulin resistance, Hispanic women have a relatively low incidence of breast cancer. High consumption of phytoestrogens has been hypothesized to be protective against breast cancer by competing as weak estrogens for receptor sites (5). A possible factor in the lower risk of breast cancer among Hispanic women is their high consumption of grains that are rich in phytoestrogens.

We hypothesize that 1) insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, will be positively associated with breast cancer, 2) the insulin resistance-breast cancer association will be more pronounced among women with high abdominal obesity or body fat content, and high levels of estrone (E1), estradiol (E2), and insulin-like growth factor-I (IGF-I), and 3) the insulin resistance-breast cancer association will be less pronounced among women consuming diets high in phytoestrogens. This proposed study may be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

1.2 Specific Aims

The specific aims of this proposed case-control study are: 1) to obtain information on breast cancer risk factors, type 2 diabetes, waist and hip circumference, body mass index (BMI), and diet, and to collect pre-diagnostic blood, 2) to assay blood for E1, E2, sex hormone-binding globulin (SHBG), insulin, glucose, IGF-I, and insulin-like growth factor binding protein 3 (IGFBP3), and 3) to perform statistical analyses to assess the association between insulin resistance and breast cancer risk, and to determine whether abdominal obesity, body fat content, E1, E2, and phytoestrogen consumption modify the effect of insulin resistance on breast cancer.

1.3 Overview of Breast Cancer in the Lower Rio Grande Valley

The Texas Cancer Registry reported breast cancer incidence rates for 1995-1997 of 100.1/100,000 for the state and 89.1/100,000 for Public Health Region (PHR) 11, which encompasses

Cameron County (2). From 1990-1999, breast cancer was the second leading cause of cancer deaths among women in Texas (23.1/100,000) and PHR 11 (19.5/100,000). Breast cancer mortality among Hispanics in PHR 11 has increased over time, evidenced by the 1990-1999 rate (17.3/100,000) that is approaching the non-Hispanic white rate (23.1/100,000). It is important to note that breast cancer incidence rates in this region may be underestimates because cancer is severely underreported and many persons seek medical care across the border in Matamoros, Mexico. A long-term goal of this partnership would be the development of a regional cancer registry for the Lower Rio Grande Valley (LRGV).

1.4 Insulin Resistance

Insulin resistance, defined as resistance to insulin-stimulated glucose uptake, has been linked to abdominal obesity, type 2 diabetes, dyslipidemias, hypertension, and cardiovascular disease (3). Seven (6-12) of eleven (13-16) studies of the association between insulin resistance or type 2 diabetes and breast cancer reported a positive association. The biological mechanism proposed to explain this association is increased levels of free IGF-I that may act synergistically with estrogen to promote mammary carcinogenesis (4). Stoll (4, 17) hypothesized that the higher risk for postmenopausal breast cancer among some ethnic groups within the US may be related to their higher genetic susceptibility to insulin resistance brought on by excess weight gain, and a high-fat, low-fiber diet. Although Hispanic women have high rates of insulin resistance (18), their high-fiber diets may counteract the effect of insulin resistance on breast cancer risk. To date, no studies of insulin resistance and breast cancer have focused on Hispanic women.

1.5 Abdominal Obesity/Body Fat Content

Obesity plays an important role in the genesis of postmenopausal breast cancer. After menopause excess body fat has been linked to increased extra-ovarian production of estrogen and decreased SHBG (19). The majority of studies that used waist-to-hip ratio as a measure of abdominal obesity found positive associations with breast cancer among all women (20-21), premenopausal women (22), and postmenopausal women (23-26). Hispanic women have the highest rate of obesity in the U.S. (27). A recent study found that weight change and obesity, defined as high body mass index greater than or equal to 30, were associated with breast cancer among all Hispanic women, but only among postmenopausal white women (28). To date, there have been no studies of abdominal obesity/body fat content and breast cancer among Hispanic women.

1.6 Endogenous Estrogen

Ovarian hormones contribute strongly to breast cancer etiology. Elevated serum estrogen levels and increased urinary excretion rates of estrone and estradiol have been found in breast cancer cases as compared with controls (29). Critical periods of estrogen exposure are thought to be *in utero*, following menarche and during perimenopause (29, 30). Factors associated with intrauterine estrogen exposure and prenatal growth, such as birth weight, have been related to breast cancer (31). Breast cancer associated with measures of postnatal growth, such as adolescent and adult weight and height, appears to differ by menopausal status (32). The different effect of weight and height on breast cancer by menopausal status may be explained, in part, by hormonal changes. Lower adult estrogen levels have been associated with low-fat, high-fiber diets (33). Non-significantly lower mean levels of E1, E2 IGF-I and IGFBP3 were found in the umbilical cord blood of Hispanic female infants compared with white female infants (34).

1.7 Insulin-like Growth Factor-I

IGF-I, a mitogen with anti-apoptotic effects on mammary cell lines (35), has been linked to premenopausal breast cancer in four studies (35-38) and to postmenopausal breast cancer in one study (39). Estrogen and IGF-I are thought to work in combination since laboratory studies have shown that

estrogen enhances the effect of IGF-I on breast cancer cell growth (40, 41). IGF-I concentrations are positively associated with height and body mass (42). Adults who were born at relatively low weights and who then become obese may have increased IGF-I and insulin levels (43). Decreased IGF-I concentrations have been associated with a low-calorie diet (44). Retinoids and vitamin D analogues also may lower IGF-I levels (45). A study of IGF-I and breast cancer survival showed a greater survival probability among women with low IGF-I levels and there was no difference between Hispanic and African-American women (46).

1.8 Phytoestrogen Consumption

Phytoestrogens, a group of biologically active compounds found in soy-based and plant-based foods, have been hypothesized to be protective against breast cancer (5). One of several mechanisms proposed for this effect is its ability to reduce estrogen activity in the breast by competing as weak estrogens for receptor sites. Phytoestrogens are classified into two main categories: isoflavones, which are found in leguminous vegetables and soybeans, and lignans, which are found in rye and fiber-rich foods. Of the dozen human studies of adult soyfood intake on breast cancer risk very few have found a statistically significant inverse association, which was limited to premenopausal women (47, 48) or another subset of women (49). While the diet of Hispanic women tends to be low in isoflavones it is high in lignans (50). A recent study of phytoestrogen consumption that included Hispanic women in San Francisco found no association with breast cancer by menopausal status or ethnicity for any of the seven phytoestrogenic compounds (51).

1.9 Research Design and Methods

This proposed study will be conducted in a mammography center. We plan to recruit 500 incident breast cancer cases and 500 control women. Breast cancer cases will be those women identified as having breast cancer through diagnostic mammography prior to undergoing treatment. Control women will be those women who are cancer free through screening mammography. In addition, control women will be at low risk of breast cancer defined as having no previous lesions that place her at higher than minimal risk, and no first-degree relative with a history of breast cancer or other hormone-related cancer.

To be eligible for this proposed study, the cases must meet the following criteria: a) newly diagnosed with primary breast cancer, b) aged 40-69 years, c) no prior history of cancer (excluding non-melanoma skin cancer), and d) resident of Cameron County at the time of diagnosis. With the exception of a), the eligibility criteria for controls will be identical to that for cases.

1.10 Recruitment Protocol, Consent, and Data Collection

Study participants will be identified through the mammography center at Valley Baptist Medical Center (VBMC) in Harlingen. This breast cancer center performs over 10,000 screening mammograms per year and is the primary source of mammography and breast cancer medical care in Cameron County. At screening, clinical staff will distribute to all women a flyer describing the study. Coding criteria established by the American College of Radiology (Breast Imaging Reporting and Data System; BI-RADS™) are used to code each screening mammogram. An uninterpretable mammogram requiring a callback is coded as 0, while interpretable mammograms are coded from 1 to 5 for the likelihood of breast cancer. Hispanic women with a suspicious (coded as 4) or highly suggestive (coded as 5) indication on screening are asked to return to the clinic for a diagnostic work-up. These women will be approached for recruitment (n=2101 per year). At least 20% of these women will be diagnosed with breast cancer, yielding 420 cases per year.

The time between mammographic screening and diagnostic services ranges between 5 and 15 days. All women with a 4 or 5 designation will be invited to participate in the study as breast cancer cases. We expect 70% of eligible 4 or 5 women to participate, yielding 294 breast cancer participants per year. Of these, 85% will be in the 40 to 69 year age range and thus eligible for this proposed study

(n=250). We will follow-up all patients to obtain data on histopathologic diagnosis of breast tumors and treatment procedures. A similar number of controls will be randomly selected from a pool of mammography-negative or benign (coded as 1 and 2, respectively) women, and frequency matched to cases on age (5-year interval). A potential control will be pre-determined before her scheduled mammographic screening.

To accomplish specific aim 1, project staff will telephone each breast cancer case and control prior to her appointment to evaluate eligibility, and to review and fully discuss the consent form. If eligible, women will be asked to complete the consent form and questionnaires during their scheduled diagnostic or screening visit. After completing the questionnaires, we will take participants' anthropometric measurements, and will measure body fat content by bioelectrical impedance using a desktop body composition analyzer. Postmenopausal women will have their blood drawn at their scheduled visit. Premenopausal women will be asked the date of their last menstrual period and the day occurring seven days prior to the onset of their next menstrual period will be used to approximate the mid-luteal phase of the menstrual cycle. The day prior to the mid-luteal phase of the cycle premenopausal women will be telephoned and reminded to observe a 10-hour fast for their blood draw at the mammography center the following morning. We estimate one hour to complete the questionnaires, and 15 minutes to collect anthropometric measurements and blood.

1.11 Questionnaires

We will collect the following anthropometric measurements: standing and sitting height, weight, waist and hip circumference, and will measure body fat content. Questionnaires will obtain information on demographics, lifestyle factors, personal health history (e.g., type 2 diabetes), medication history (e.g., estrogen and insulin), menstrual and pregnancy history, medication use, family history of cancer and other chronic diseases, and adult weight history (see pages 78-96 for a sample questionnaire). The National Cancer Institute Health Habits and History Questionnaire, modified for use in this population and to collect phytoestrogen-rich foods, will collect dietary information one year prior to the cancer diagnosis for cases and an equivalent date for controls. Women will be classified as premenopausal, perimenopausal and postmenopausal based on the number of months or years since their last menstrual cycle.

1.12 Blood Collection and E1, E2, SHBG, Insulin, Glucose, IGF-I and IGFBP3 Assays

Using standard, sterile phlebotomy procedures, a 10-hour fasting blood specimen will be drawn from the antecubital vein into two tubes – one with ethylenediamine-tetraacetic acid (EDTA) and one with no anti-coagulant. The date and time of blood collection and the day of last menstrual period will be recorded. Blood samples will be placed in a cooler and transported to South Texas Hospital where they will be refrigerated (0-4° C) and centrifuged within 2 hours of collection (3000 g for 15 minutes). Serum and plasma will be aliquoted into five 1-ml cryo-vials and stored at -70° C until analysis. Although we are only collecting one blood sample from each woman, one sample may reflect longer term circulating concentrations of these measures.

To accomplish specific aim 2, we will determine the insulin in plasma by radioimmunoassay (RIA), the E1 and E2 level in serum by RIA, the SHBG level in serum by double antibody RIA, and the IGF-I and IGFBP3 in serum by immunoradiometric assay (IRMA) with reagents from Diagnostic Systems Laboratory (Webster, TX). Plasma glucose will be measured using the glucose oxidase method on a Beckman Instruments glucose analyzer (Fullerton, CA). All assays will be performed by staff of the South Texas Hospital located in Harlingen.

1.13 Statistical Analysis

To accomplish specific aim 3, we will conduct statistical analyses. The focus of the analysis is the relationship between insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, and the risk of breast cancer. Women will be defined as insulin resistant if they are: 1) in the

upper quartile of the homeostasis model assessment for insulin resistance ($HOMA_{IR}$) or 2) have type 2 diabetes based on self-reported history or an elevated fasting glucose. We will use the $HOMA_{IR}$ equation developed by Matthews et al. (52) ($HOMA_{IR}$=fasting insulin (μU/ml)/[22.5 x $e^{-ln(glucose\ [mmol/l])}$]) since it's more highly correlated with insulin resistance derived from the hyperinsulinemic-euglycemic clamp than fasting insulin alone (53). Self-reported history of type 2 diabetes will be indicative of insulin resistance since women taking oral hypoglycemics should not have an elevated glucose concentration. Type 2 diabetes tends to be undiagnosed due to the gradual development of symptoms (54); therefore, fasting plasma glucose of ≥ 126 mg/dl will also be used to define type 2 diabetes (55).

Unconditional logistic regression will be used to estimate the risk of breast cancer associated with insulin resistance in the case and control groups, while accounting for confounding and effect modification (56). Covariates to be examined as potential confounders and effect modifiers of the relationship between insulin resistance and breast cancer risk are age, date and time of blood draw, fasting status at time of blood draw, assay batch, family history of breast cancer and other chronic conditions (e.g., diabetes, cardiovascular disease), age at menarche, age at menopause, parity, age at first live birth, use of exogenous estrogens and insulin, smoking, and alcohol use. Variables will be considered confounders of the relationship between insulin resistance and breast cancer risk if their addition to the model changes the unadjusted odds ratio by 10 percent or more (57). Interaction terms, the product of insulin resistance and putative effect modifiers, will be added to logistic regression models to test for effect modification by abdominal obesity or body fat content, elevated levels of E1, E2 and IGF-I, and high phytoestrogen consumption (58). In addition to measuring body fat content, we will use minimum waist circumference adjusted for BMI (kg/m^2) to define abdominal obesity, since it appears to be more accurate than waist-to-hip ratio (59). The upper quartile of biochemical measures and phytoestrogen consumption in the control group will provide evidence of elevated levels.

1.14 Sample Size and Power Considerations

Table 1 presents the power this proposed study will have to detect odds ratios of breast cancer of 1.5, 2.0 and 2.5 for insulin resistance categories. We assume an alpha level of 0.05. Using the upper quartile of $HOMA_{IR}$ to define insulin resistance, we should have adequate power to evaluate the main effects and some joint effects for stronger associations. Using type 2 diabetes to define insulin resistance, we should have adequate power for the main effects, but limited power to detect weak associations for joint effects.

Table 1. Power to detect odds ratios of breast cancer of 1.5, 2.0 and 2.5 for insulin resistance categories

	Proportion of Controls Exposed	Odds ratios		
		1.5	2.0	2.5
Upper quartile of $HOMA_{IR}$	.25	.83	.99	.99
Type 2 diabetes (38)	.06	.38	.85	.98

1.15 Potential Limitations

The $HOMA_{IR}$ model based on fasting serum insulin and glucose is a surrogate measure of insulin resistance (52); however, in a study of Pima Indians the correlation with the hyperinsulinemic-euglycemic clamp was –0.62 (53). Studies that utilize self-administered questionnaires are potentially limited by selection bias and recall bias. The questionnaires have been designed to minimize non-response, and rigorous tracking and follow-up procedures will be implemented to attain the projected response rates of 70%. Although we are using biochemical measures which are not subject to recall bias for the majority of exposures and effect modifiers under study, some of the biochemical measures may be altered by cancer status. This hypothesis is fairly new and has not been popularized; therefore, it is unlikely that breast cancer cases will respond differently than controls.

1.16 Potential Strengths

This proposed study will attempt to include all women presenting for a diagnostic mammogram, and a sample of women seen for screening mammograms from the primary mammography center in Cameron County. With a 70% response rate, results will be generalizable to Hispanic women aged 40-69 who reside in the county. The potential benefit of identifying an association between insulin resistance and breast cancer is feasible at low cost. Information from this proposed study will be used to submit larger grants for additional funding to investigate factors associated with decreased breast cancer risk among Hispanic women.

1.17 Potential Future Studies

We will store blood samples for genetic testing in future studies. Jernstrom et al. (60) identified polymorphic variants of the CYP3A4, IGF1 and AIB1 genes that may account for the higher IGF-I levels among African-American compared with white women. We will examine whether these variants are common among our population of Hispanic women. Given sufficient sample size we would like to investigate gene-environment interactions, such as the various combinations of CYP3A4, IGF1, AIB1, insulin resistance, abdominal obesity, body fat content, endogenous estrogen, IGF-I and phytoestrogen consumption, and their association with breast cancer.

2. Collaborative Arrangement

The collaborative arrangement for the HBCU/MI Partnership Training Award will consist of three UTB faculty with no history of breast cancer funding, and six UTSPH faculty with funding histories in breast and others cancers. Specific goals of the partnership are: 1) to develop a regional cancer registry, 2) to build infrastructure to conduct case-control studies of breast cancer, 3) to initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) to establish an outstanding breast cancer research program.

2.1 Interaction between UTB and UTSPH

The training program will provide the opportunity for UTB faculty to benefit from the training and mentoring of researchers from the UTSPH, at the Brownsville regional campus and at the main campus in Houston. Two of the six UTSPH faculty are located in Brownsville and will provide on-site training. The remaining four UTSPH faculty will provide training via interactive television (ITV) and quarterly visits to Brownsville. The three UTB faculty, six UTSPH faculty and members of the Cameron County medical and lay community will form an advisory committee for the project.

2.2 Overview of UTSPH

Although the University of Texas-Houston School of Public Health is the collaborating institution, this overview will focus on the Brownsville regional campus where the Co-PI is located and where the majority of the training will take place. In 1998, State legislation was passed that created the Lower Rio Grande Valley Regional Academic Health Center consisting of a medical school in Harlingen, basic science school in Edinburg, and public health school in Brownsville. This creation will contribute greatly toward providing educational opportunities for medical, biological science, and public health students in the LRGV. In 1999, UTSPH offered its first classes on the UTB campus in Brownsville. The only UTSPH degree offered in Brownsville is the Master's of Public Health (MPH) with options in Behavioral Sciences, Biological Sciences, Biometry, Environmental and Occupational Health Sciences, Epidemiology, and Management and Policy Sciences. The Brownsville regional campus works cooperatively with the UTB Master of Science in Public Health Nursing program by providing classes in the core areas of public health. The UTSPH at Brownsville recently moved into new facilities in 2002, which includes two ITV classrooms with state-of-the-art equipment enabling students in Brownsville to participate in classes offered by faculty in Houston and other regional

campuses. About 3000 square feet of laboratory space will be completed which will accommodate environmental health, genetic and serological studies as needed. There will be facilities for tissue culture, viral and bacteriological cultures, polymerase chain reaction and serology. Given that UTSPH, Brownsville regional campus has only been in existence since January 2001, we present demographic characteristics of UTSPH students and faculty from the campuses located in Houston, Brownsville, Dallas, El Paso and San Antonio combined. Of the 901 students and 139 faculty at UTSPH, the percentage of Hispanics is 16.1% and 8.6%, respectively. The percentage of females is higher among UTSPH students (69.6%) than UTB students (61.0%), but identical for the two faculties (44%).

2.3 Qualifications of UTSPH Faculty

Dr. Maureen Sanderson, Co-PI, is an Associate Professor of Epidemiology at the Brownsville regional campus of the UTSPH. She has been PI for etiologic studies of breast and prostate cancer since 1997, and has extensive experience in the design, implementation, and evaluation of population-based case-control studies. She is a current recipient of a Department of Defense Career Development Award (CDA) to investigate interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. To date, Dr. Sanderson has been investigating these relationships using preexisting data; however, this proposed study would accomplish one aim of the CDA to conduct a case-control study of the insulin resistance-breast cancer relationship. As Co-PI, she will assist Dr. Peltz with project leadership, and with ensuring the scientific oversight of research activities. In addition to teaching introductory epidemiology and co-teaching nutritional epidemiology, she will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. Sally Vernon, Co-Investigator, is a Professor of Epidemiology and Behavioral Sciences at UTSPH-H. She has been PI for studies of breast and colorectal cancer prevention and control since 1987, and has extensive experience combining quantitative and qualitative methods in these studies. She recently began a 5-year study, funded by the National Cancer Institute (NCI), to develop and evaluate an intervention to encourage adherence to mammography screening guidelines in a nationally representative sample of women veterans. Currently, Dr. Vernon is mentoring several junior UTSPH faculty members, and she received a minority supplement to her NCI grant on Breast Cancer Screening in Women Veterans for Dr. Cynthia Warrick. She will provide training expertise to the project. In addition to teaching proposal development, she will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. R. Sue Day, Co-Investigator, is an Associate Professor of Epidemiology at the UTSPH-H. She has been PI for studies of cancer and cardiovascular disease since 1988, and has extensive experience assessing nutritional status in cancer case-control studies. Dr. Day acted as consultant to the New Mexico Cancer Registry for a breast cancer study among Hispanic women, and participated in methods development, and data collection, management and analysis issues. She will provide nutritional status assessment expertise to the project. In addition to teaching field epidemiology and co-teaching nutritional epidemiology, she will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. Guillermo Tortolero-Luna, Co-Investigator, is an Associate Professor of Epidemiology at the UTSPH-H. He has been PI for studies of cancer etiology and prevention since 1992, and has expertise in cancer biology. He and Dr. Fernandez are funded by the Centers for Disease Control and Prevention to study the utilization of mammography screening and the predictors of appropriate screening among low-income Hispanic women, including farmworker women in the Texas-Mexico border area. In addition to teaching cancer epidemiology, he will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. Maria Fernandez, Co-Investigator, is an Assistant Professor of Behavioral Sciences at the UTSPH-H. She has been PI of studies health disparities among Hispanics since 1996, and has expertise in behavioral sciences as it relates to breast and cervical cancer screening. Currently, she is the PI on an NCI funded Preventive Oncology Academic Award focusing on repeat mammography among low-

income and minority women. Dr. Vernon is one of her mentors on this award. She will be instrumental in the evaluation of the project. In addition to teaching intervention mapping, she will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. Adriana Perez, Co-Investigator, is an Assistant Professor of Biometry at UTSPH, Brownsville regional campus. She has conducted research in the area of clinical trials of stomach cancer, intensive care units, asthma and depression, and has extensive experience collaborating in clinical research in Hispanic populations. She will provide biostatistical expertise to the project. In addition to teaching introductory biometry, she will share responsibility for reviewing UTB proposals and co-authoring scientific papers based on findings from the study.

3. Training Program

The HBCU/MI Partnership Training Award will assist UTB in its' goal of developing necessary infrastructure for research in breast cancer and related areas. Since UTB has only been in existence for 10 years it is not surprising that very few faculty (24%) are funded to conduct research. In addition to encouraging current faculty members to conduct research, UTB is actively recruiting faculty that have experience conducting research. UTB faculty who have undergone training through this partnership can then work with other colleagues to encourage and mentor future breast cancer researchers at the university.

3.1 Development of Successful Breast Cancer Research Program

The locations of UTB and UTSPH, Brownsville regional campus on the same campus will facilitate the development and maintenance of an outstanding breast cancer research program. In addition, the PI from UTB and Co-PI from UTSPH have mutual interests in studying reasons why Hispanic women possess a number of breast cancer risk factors and yet have a fairly low incidence of the disease. Very few breast cancer studies have focused on Hispanic women; however, the identification of protective factors against breast cancer may contribute to our understanding of the biological mechanisms of the disease. UTB administration understand this contribution and are committed to the success of this program.

The average course load for UTB faculty is four to five courses per semester. Heavy course loads and limited assistance from staff or students has prohibited most UTB faculty from engaging in research activities. Although UTB has yet to institute a release time policy to allow faculty time off from teaching to participate in research, the President and Provost/Vice President of Academic Affairs have concurred that a policy of release time be developed as part of this program. The respective deans and the provost have submitted a letter of support ensuring release time for UTB faculty to complete the training program. Faculty will be allowed time to participate in training seminars, conferences and educational events relevant to the continued development of research at the university.

3.2 Overview of UTB

In 1991, the Texas Legislature passed legislation that created UTB. The partnership combined a junior college, the first institution of higher education in the LRGV created in 1926, with a free-standing upper-level university. As "America's first Community University," the mission of the UTB partnership is to provide accessible, affordable, post-secondary education of high quality, to conduct research, which expands knowledge, and to present programs of continuing education, public service, and cultural value to meet the needs of the community. In November 1996, UT System Board of Regents approved the university's application for single accreditation and in May 1997 both boards signed the agreement. The partnership used its combined resources to continue creating new degree programs, serve a growing student population, and to expand campus infrastructure to serve the local community. UTB currently occupies some 350 acres adjacent to the US/Mexico border on the Gulf of Mexico near Tamaulipas, Mexico. UTB is the only public university in Texas that offers certificate through master's degree level

with cooperative agreements offering options for doctoral programs. Of the 9,360 students, 92.6 % are Hispanic, 61.0% are female, the average age is 25.6 years, 74.9% first generation college students, and over 80% of students require some form of financial assistance. Over one-third of UTB's 251 faculty are Hispanic (37.5%) and 44% are female.

3.3 Qualifications of UTB Faculty

Dr. Gerson Peltz, PI, is a newly appointed Professor of Biology at UTB. This is his first academic position, having staffed (1986-2001) and chaired the internal medicine department of the Brazilian National Cancer Institute (1995-2001). He has extensive experience in enteral/parenteral nutrition and cancer, and has worked on numerous cancer-related research projects. Dr. Peltz was funded by the Brazilian National Institute of Cancer and Texas A & M University from 1998-2000 to investigate the role of lycopene in the chemoprevention of prostate cancer. He recently submitted a small proposal to investigate the roles phytoestrogen consumption and body fat content play in breast cancer risk among Hispanic women that was not recommended for funding. As part of the training program he will complete the MPH with a focus on epidemiology to enable him to conduct etiologic breast cancer research independently. As PI, Dr. Peltz will provide overall direction and leadership to the project, and will be responsible for ensuring the scientific oversight of research activities, supervision of all project personnel and management of project resources. He will take the lead on writing UTB proposals, and will share responsibility for co-authoring scientific papers based on findings from the study.

Dr. Nancy McGowan, Co-Investigator, is an Associate Professor of Nursing in the Associate Degree in Nursing program at UTB. She received her PhD in Nursing in 2001 and completed a study of processes of change, smoking behavior and breast cancer among Mexican American women for her dissertation. Dr. McGowan has extensive experience supervising nursing students in clinical settings and will be instrumental in recruiting patients for the study. She is currently certified as an Emergency Nurse Pediatric Provider, Advanced Cardiac Life Support Provider and Instructor, and Trauma Nurse Care Provider. Dr. McGowan will audit courses within the MPH program to gain knowledge of cancer research methods. She will share responsibility for writing UTB proposals and co-authoring scientific papers based on findings from the study.

Dr. Matthew Johnson, Co-Investigator, is an Assistant Professor of Psychology at UTB. He received his PhD in Experimental Psychology with a Cognitive Emphasis in 1998 and completed a study on learning strategy skills as predictors of academic success for his dissertation. Dr. Johnson has extensive experience conducting psychometric testing, and will be instrumental in developing a questionnaire appropriate for use with the local Hispanic population. He received a UTB teaching, learning and technology mini-grant in 2001 to investigate cognition. Dr. Johnson will audit courses within the MPH program to gain knowledge of cancer research methods. He will share responsibility for writing UTB proposals and co-authoring scientific papers based on findings from the study.

3.4 Overview of Training Program

This proposal is envisioned as occurring in two phases the Training Phase and the Investigation Phase. UTB faculty will undergo intensive training provided by UTSPH faculty during year 1. Additional training will take place in subsequent years. To reinforce training, faculty from UTB and UTSPH will conduct a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 and 3. Under the guidance of UTSPH faculty, UTB faculty will submit grants for additional funding using the breast cancer study as preliminary data in year 4.

3.5 Training Phase

Dr. Peltz will take MPH courses for credit toward his MPH degree. A total of 36 credits are required. It is anticipated that 1-2 courses will be completed a semester thus requiring 2-3 years for the completion of the degree. The core courses in public health are epidemiology (4 credits), biostatistics (4

credits), behavioral sciences (3 credits), environmental health (4 credits) and management and policy sciences (3 credits). In addition, elective courses will include proposal development (3 credits), cancer epidemiology (3 credits), nutrition epidemiology (3 credits), field epidemiology (3 credits), and intervention mapping (3 credits). All students must complete a public health practicum (3 credits) and thesis (3 credits). The core courses and nutrition epidemiology course will be taught in Brownsville and the elective courses will be available via ITV from Houston. Drs. McGowan and Johnson will be highly encouraged to audit as many of these courses as possible.

Additional activities to be completed by UTB and UTSPH faculty during the training phase include: 1) liaise with local medical providers, health clinics and state health agencies to encourage reporting of breast cancer to the Texas Cancer Registry, 2) identify sites for data collection with local health providers and health clinics, 3) develop a questionnaire for use with the local Hispanic population, 4) after consultation with local health providers design a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw, 5) initiate institutional review board approval through local and federal channels, and 6) pilot test study methods and revise the study design as needed.

3.6 Investigation Phase

Details of the clinic-based case-control study are presented under the background section. Additional activities to be completed by UTB and UTSPH faculty during the investigation phase include: 1) consult with local health providers and health clinics regarding the reporting mechanism for breast cancer and provide training as needed, 2) expand data collection to cancers other than breast cancer as a means of developing a regional LRGV cancer registry, 3) disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics, 4) report findings and recommendations in peer-reviewed medical literature, and 5) submit proposals to conduct larger population-based case-control studies of breast cancer in the LRGV.

4. Communication

UTB and UTSPH, Brownsville regional campus faculty will meet weekly to discuss the progress of the training program, and to address areas in need of improvement. The training program advisory committee, consisting of three UTB faculty, six UTSPH faculty and members of the Cameron County medical and lay community will meet in Brownsville on a quarterly basis. Should problems arise more frequent meetings of UTB and UTSPH faculty will be conducted via ITV. Each UTB faculty will meet at the end of every semester in Houston (3 times per year) with their academic advisory committee consisting of one or more UTSPH faculty. While in Houston UTB faculty will have the option of attending seminars or related courses. It is crucial that investigators have the support and input of local health providers; therefore, periodic meetings will be held with local oncologists and other medical professionals.

Reports will be completed on a quarterly basis for distribution to members of the advisory committee. Information on the progress of the training program will include work performed, plans for next quarter, problems encountered and products. As indicated above, should problems arise they will be resolved as soon as possible by meeting with UTB and UTSPH faculty via ITV. Information specific to the progress of the breast cancer study will include institutional review board approval, completion of the study protocol and questionnaire, contact of cases and controls, pilot testing study methods and response rates. These reports will be shared with the deans of the respective institutions. Information from these reports will be complied and submitted to the Department of Defense as annual reports.

To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

Abbreviations

BMI – Body mass index

CDA - Career development award

E1 - Estrone

E2 – Estradiol

EDTA - Ethylenediamine-tetraacetic acid

$HOMA_{IR}$ – Homeostasis model assessment for insulin resistance

IGF-I - Insulin-like growth factor-I

IGFBP3 – Insulin-like growth factor binding protein-3

IRMA – Immunoradiometric assay

ITV – Interactive television

LRGV – Lower Rio Grande Valley

MPH – Masters of Public Health

NCI – National Cancer Institute

PHR – Public Health Region

RIA – Radioimmunoassay

SHBG – Sex hormone binding globulin

UTB – University of Texas at Brownsville

UTSPH – University of Texas-Houston School of Public Health

VBMC – Valley Baptist Medical Center

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Appendix F

SOYFOOD INTAKE, INSULIN-LIKE GROWTH FACTOR-I AND BREAST CANCER RISK

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Previous reports from the Shanghai Breast Cancer Study (SBCS) suggested that adolescent and adult soyfood intake was inversely related to the risk of breast cancer, and elevated levels of insulin-like growth factor I (IGF-I) were associated with an increased risk of breast cancer. In the current study, we assessed whether IGF-I levels modified the effect of soyfood intake on breast cancer risk.

The SBCS is a population-based case-control study of breast cancer among women age 25 to 64 conducted between 1996 and 1998 in urban Shanghai. In-person interviews were completed with 1459 incident breast cancer cases ascertained through a population-based cancer registry, and 1556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). This analysis is restricted to the 300 cases and 300 matched controls for whom information on IGF-I levels was available.

After adjustment for confounding, the protective effect of soyfood intake was only observed among women with a lower IGF-I level (OR= 0.56 for adolescent and OR=0.68 for adult soyfood intake) but not for women with a higher IGF-I level (OR=1.41 for adolescent and OR=2.12 for adult soyfood intake), although none of the point estimates was statistically significant, possibly due to the small sample size. Higher IGF-I level was associated with an increased risk of breast cancer regardless of the level of soyfood intake.

Our results appear to suggest that the effect of soyfood intake on breast cancer risk is dependent on adult IGF-I levels. Further studies are needed to confirm our finding and to understand the biological mechanism of this possible interaction. Should IGF-I levels prove to be associated with breast cancer in other populations, the possibility that soyfood intake may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

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Insulin-Like Growth Factor-I, Soyfood Intake and Breast Cancer Risk

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Running title: IGF-I, soyfood intake and breast cancer risk

Abstract

Objective: Previous studies have found that estrogen enhances the effect of IGF-I levels on breast cancer cell growth. Participants in the Shanghai Breast Cancer Study (SBCS) consume large amounts of soyfood that is high in isoflavones, which act as weak estrogens and as anti-estrogens. In the current study, we assessed whether soyfood intake modified the effect of IGF-I levels on breast cancer risk.

Methods: The SBCS is a population-based case-control study of breast cancer among women age 25 to 64 conducted between 1996 and 1998 in urban Shanghai. In-person interviews were completed with 1459 incident breast cancer cases ascertained through a population-based cancer registry, and 1556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). This analysis is restricted to the 397 cases and 397 matched controls for whom information on IGF-I levels was available.

Results: High IGF-I levels were associated with non-significantly elevated risks of breast cancer regardless of the level of soyfood intake. There was little or no interaction among women diagnosed premenopausally (OR=1.53 for high IGF-I and low soyfood; OR=1.68 for high IGF-I and high soyfood), but a non-significant negative interaction among women diagnosed postmenopausally (OR=2.62 for high IGF-I and low soyfood; OR=1.62 for high IGF-I and high soyfood) (p for interaction=0.235).

Conclusion: Our results suggest that soyfood intake may modify the effect of IGF-I levels on postmenopausal breast cancer risk. Further studies are needed to confirm our finding and to understand the biological mechanism of this possible interaction.

Introduction

Insulin-like growth factor-I (IGF-I) is thought to play a role in breast cancer due to its anti-apoptotic effects on mammary cell lines.[1] IGF-I has been positively associated with premenopausal breast cancer in four studies of Caucasian women,[2-5] and with postmenopausal breast cancer in one study of African-American women.[6] A previous report from the present study, the Shanghai Breast Cancer Study (SBCS), showed that elevated levels of IGF-I were associated with an increased risk of breast cancer which was more pronounced among women diagnosed premenopausally and among women with a high body mass index or waist-to-hip ratio.[7] IGF-I and estrogen may work in combination to cause breast cancer since laboratory studies have shown that estrogen enhances the effect of IGF-I on breast cancer cell growth.[8, 9]

High consumption of soyfood during adulthood has been hypothesized to be protective against breast cancer. One of several mechanisms proposed for this effect is its richness in isoflavones, which may reduce estrogen activity in the breast by competing as weak estrogens for receptor sites.[10] Isoflavones may also act as anti-estrogens by decreasing ovarian hormones[11] and by increasing sex hormone binding globulin.[12] Of the 13 human studies of adult soyfood intake on breast cancer risk only those conducted among Asian or Asian-American populations, who consume large amounts of soy, have found statistically significant inverse associations. In one of the studies the reduction in breast cancer risk was seen among all women,[13] while two studies were limited to premenopausal women,[14, 15] and a fourth study was limited to another subset of women.[16] A previous report from the present study found that adult soyfood intake was associated with a reduced risk for women with a higher body mass index or with a estrogen receptor (ER)/progesterone receptor (PR) positive breast cancer.[16]

In addition to their effect as weak estrogens and anti-estrogens, isoflavones may reduce cancer risk by inhibiting cancer cell growth stimulated by growth factors.[17] Other proposed mechanisms for the protective effect of isoflavones on cancer are their ability to inhibit topoisomerase I and II,[10] proteases,[18] tyrosine kinases,[10] inositol phosphate,[19] and angiogenesis.[10] Additional chemopreventive properties of isoflavones include antioxidation and immune enhancement.[20] In animal studies, isoflavones have been associated with reduced numbers of breast tumors.[10, 21]

Soyfood, consumed in relatively high quantities in Shanghai, acts as a weak estrogen and as an anti-estrogen and may work in combination with IGF-I levels to cause breast cancer. Based on these factors we decided to assess whether soyfood intake modified the effect of IGF-I levels on breast cancer risk.

Materials and Methods

Detailed methods of this population-based case-control study appeared elsewhere.[22] Briefly, all women age 25 to 64 years who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer. A total of 1,459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of potentially eligible cases, 109 refused (6.8%), 17 died prior to the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent adult residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-year interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990 through 1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1,556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 potentially eligible controls (9.6%) refused participation. Two women died prior to the interview and were excluded.

The study was approved by relevant institutional review boards in Shanghai and the United States. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The subject questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives and hormone replacement therapy, diet, physical activity, lifestyle factors, and body size. Adult soy

consumption in the past 5 years was collected using a 76-item food frequency questionnaire. Detailed methods of the calculation of soy protein equivalence appears elsewhere.[16] Briefly, foods on the questionnaire used to calculate soy protein equivalence based on the Chinese Food Composition Table[23] were tofu, soy milk, fresh soybeans, dried soybeans, soybean sprouts and other soy products. Weights were applied to these foods to account for the edible portion, the mixture of non soyfoods and seasonal variation. The soyfood items were then summed to estimate total soy protein.

After completing the interview, over 80 percent of women provided fasting blood samples (1193 cases, 1310 controls). Detailed methods of blood collection and testing appeared elsewhere.[7] Briefly, plasma was separated from samples and stored at -70°C within 6 hours of collection. This analysis is restricted to the 397 cases whose blood samples were collected prior to therapy and 397 controls individually matched on age (within 5 years), date of blood collection (within 30 days) and menopausal status for whom information on IGF-I levels was available. Plasma IGF-I concentration was determined with an enzyme-linked immunosorbent assay kit available from DSL, Inc. (Webster, TX). Previous studies of IGF-I and cancer have used these methods with good reproducibility.[4, 24] The intraassay and interassay precisions were 1.5-3.4% and 1.5-8.5% of the coefficient of variation.[25]

We used conditional logistic regression to estimate the relative risk of breast cancer associated with IGF-I levels while controlling for confounders.[26] Tertile distributions among controls were used to categorize main effects, while the joint effects analysis used median distributions among controls. To assess whether soyfood intake modified the effect of IGF-I levels on breast cancer risk we estimated the stratum-specific odds ratios among the group with high levels of IGF-I and soyfood intake for comparison with the group with high IGF-I levels and

low soyfood intake by dividing the OR of high IGF and high soy intake with the OR of high IGF and low soy intake. All variables were entered into models as dummy variables. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables.

Results

Table 1 compares known breast cancer risk factors of cases and controls. Compared to controls breast cancer cases were more likely to have a history of fibroadenoma, to drink alcohol regularly, to exercise, to have a higher body mass index (BMI), and to have a later age at first birth. Subsequent analyses were adjusted for all of the preceding variables and age, education, family history of breast cancer, waist-to-hip ratio, menarcheal age, parity, menopausal status, and total energy intake. Analyses are presented for all women and separately by menopausal status since the effect of some hormonal and growth factor exposures on breast cancer risk is thought to differ by menopausal status.

Table 2 presents the odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with tertiles of soyfood intake in the parent study and the present study. Neither the parent study nor the present study found an association for adult intake of soyfood among all women. There was an indication that high soyfood intake was related to a non-statistically significant reduced risk of postmenopausal breast cancer (OR=0.55, 95% CI 0.22-1.36).

Risk of breast cancer associated with tertiles of IGF-I levels are shown in Table 3. There was evidence of a significant trend of increasing risk with increasing IGF-I levels among all women and by menopausal status. The elevation in risk for the highest IGF-I level relative to the lowest IGF-I level appeared to be more pronounced among women diagnosed postmenopausally (OR=3.03, 95% CI 1.18-7.75) than among women diagnosed premenopausally (OR=2.30, 95% CI 1.28-4.13). The confidence intervals surrounding these point estimates were quite wide arguing for cautious interpretation of these findings.

Median soyfood intake among premenopausal and postmenopausal controls was similar (9.3); however, median IGF-I levels were higher among premenopausal controls (176.3) than among postmenopausal controls (119.6). There was no correlation between soyfood intake and IGF-I levels in the control group of all women ($r = -0.003$, $p = 0.95$) nor after stratifying by menopausal status (premenopausal: $r = 0.003$, $p = 0.95$; postmenopausal: $r = -0.01$, $p = 0.91$).

Table 4 shows the effect of increasing IGF-I levels on breast cancer risk among women with low and high levels of soyfood intake among all women and by menopausal status. The referent group is women whose IGF-I level and soyfood intake was less than the median. High IGF-I levels were associated with non-significant increases in risk regardless of level of soyfood intake. We divided the odds ratio for the group with high levels of IGF-I and soyfood intake by the odds ratio for the group with low IGF-I levels and high soyfood intake for comparison with the stratum-specific odds ratio for high IGF-I levels and low soyfood intake. There was little or no interaction among women diagnosed premenopausally (OR=1.53 for high IGF-I and low soyfood; OR=1.68 for high IGF-I and high soyfood), but a non-significant negative interaction among women diagnosed postmenopausally (OR=2.62 for high IGF-I and low soyfood; OR=1.62 for high IGF-I and high soyfood) (p for interaction=0.235).

Discussion

We found an indication that soyfood intake may modify the effect of elevated IGF-I levels on postmenopausal breast cancer risk, but not on premenopausal breast cancer risk. The mechanism of the non-significant negative interaction between soyfood intake and IGF-I levels on breast cancer risk among postmenopausal women is unknown, but could be due to soy inhibiting tumor cell growth stimulated by growth factors.[17] Genistein, the primary isoflavone, has been shown to inhibit the proliferation of breast cancer cells stimulated by epidermal growth factor (EGF).[17] In contrast, EGF and IGF-I have been shown to work synergistically to stimulate breast cancer cell growth.[27]

There was no evidence of a soyfood—IGF-I level interaction among women diagnosed premenopausally probably due to the lower consumption of soyfood among premenopausal women. The significant inverse associations between soyfood intake and breast cancer risk have only been observed among Asian and Asian-American populations who consume large quantities of soy.[13-16] In only one of those studies was the effect seen among all women, which may indicate a threshold level of soyfood is necessary to see a reduction in breast cancer risk.

Laboratory studies have shown that estrogen increased the effect of IGF-I on breast cancer cell growth.[8,9] However, we found that the odds ratio for the highest tertile of IGF-I was more pronounced among postmenopausal women than premenopausal women. The non-significant negative interaction between soyfood and IGF-I level among postmenopausal women could not be explained by the estrogen-IGF—I hypothesis. However, we did not find that soyfood intake was correlated with estradiol ($r = -0.14$, $p = 0.12$), estrone ($r = 0.04$, $p = 0.65$) or sex hormone binding globulin ($r = -0.03$, $p = 0.74$) levels among postmenopausal controls in this

study, suggesting that the soy intake level among the study population may not be high enough to alter the estrogen level. More studies are needed to better understand the combined effect of estrogen and growth factor on breast cancer.

This study was not without limitations. Data on IGF-I levels were available for a subgroup of women, reducing statistical power to detect effect modification. IGF-I levels among healthy women in our population were lower than those among Caucasian women in the Nurses' Health Study[4] somewhat limiting the generalizability of our results. Reporting of soyfood intake is prone to misclassification. A recently completed dietary validation study showed that correlation of soy protein intake derived from the food frequency questionnaire that we used in the study and the mean of multiple 24-hour dietary recalls was 0.49 (Shu, 2002). Misclassification in assessing soyfood intake may have compromised our ability to investigate the interactive effect of soyfood intake and IGF-I. Change of dietary habits overtime, particularly after cancer diagnosis, is another concern. A supplementary questionnaire was completed with the majority of women asking whether their soyfood consumption in the past week was similar to their consumption in the past 5 years.[16] Results comparing women whose diets hadn't changed with all women were slightly more pronounced, but fairly comparable.

Although in vitro studies of breast cancer have investigated the interaction between estrogen and IGF-I levels,[8, 9] ours is the first in vivo study to investigate the interaction between soyfood, a weak estrogen and anti-estrogen, and IGF-I levels. The relatively high soyfood consumption among our population compared to the rest of the world made this analysis possible. Additional strengths of this study are its population-based nature and high response rates among subjects (cases: 91%; controls: 90%) which minimizes selection bias. We adjusted for known breast cancer risk factors, and evaluated the IGF-I level, soyfood intake and breast

cancer associations in conjunction with menopausal status, a suspected effect modifier of these relations.

In summary, our results suggest that soyfood intake may modify the effect of IGF-I levels on postmenopausal breast cancer risk. Further studies with larger sample sizes are needed to confirm our finding and to understand the biological mechanism of this possible interaction.

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Table 1. Comparison of cases and controls for selected risk factors

	Cases[a] (n = 397)	Controls[a] (n = 397)	P-value
Age	47.8 ± 7.9	47.6 ± 8.0	0.83
Education (%)			
No formal education	12.6	14.6	
Elementary education	44.3	43.1	
Middle + high school	30.5	31.5	
Profession, college and above	12.6	10.8	0.74
Per capita income (Yuan) (%)			
<4000	17.4	17.6	
4000-5999	31.5	29.7	
6000-7999	12.1	13.9	
8000-8999	21.9	25.7	
≥9000	17.1	13.1	0.40
Breast cancer in first degree relatives (%)	3.0	1.5	0.15
Ever had breast fibroadenoma (%)	9.1	4.8	0.02
Regular alcohol drinker (%)	5.6	2.3	0.02
Ever used oral contraceptives (%)	21.9	25.4	0.24
Ever used hormone replacement therapy (%)	3.5	3.0	0.68
Exercised regularly as adult (%)	20.9	29.7	<0.01
Body mass index	23.5 ± 3.2	23.0 ± 3.3	0.02
Waist-to-hip ratio	0.80 ± 0.1	0.80 ± 0.1	0.21
Nulliparous (%)	4.0	3.3	0.57
Number of live births[b]	1.5 ± 0.8	1.5 ± 0.8	0.98
Age at first live birth[b] (years)	27.3 ± 4.1	26.7 ± 3.9	0.03
Months of breast feeding[c]	15.2 ± 12.9	15.9 ± 13.4	0.47
Menarcheal age (years)	14.7 ± 1.7	14.9 ± 1.7	0.12
Menopausal age[d] (years)	48.5 ± 4.5	47.8 ± 4.5	0.15
Height (cm)	160.6 ± 37.0	160.6 ± 42.5	0.99
Usual total energy intake (kcal/day)	1905.9 ± 470.9	1862.4 ± 431.9	0.18

Subjects with missing values were excluded from the analysis.
[a] Unless otherwise specified, mean ± SD are presented.
[b] Among women who had live births.

[c] Among women who ever breast fed their children.
[d] Among menopausal women.

Table 2. Odds ratios of breast cancer associated with tertiles of soyfood intake in the parent study and the present study, for all women and by menopausal status

	Parent Study			Present Study		
	Case/Ctrl	OR[a]	(95% CI)	Case/Ctrl	OR[a]	(95% CI)
			All women			
Soyfood intake (g/day)						
T1[b]	448/519	1.00	Referent	132/133	1.00	Referent
T2	544/518	1.25	(1.04-1.50)	135/131	1.17	(0.80-1.71)
T3	467/519	0.99	(0.81-1.21)	130/133	0.96	(0.64-1.44)
P trend		p=0.296			p=0.111	
			Premenopausal women			
Soyfood intake (g/day)						
T1[c]	303/330	1.00	Referent	90/84	1.00	Referent
T2	333/329	1.09	(0.86-1.37)	75/84	0.96	(0.57-1.63)
T3	316/331	1.01	(0.79-1.29)	85/84	1.21	(0.70-2.08)
P trend		p=0.865			p=0.783	
			Postmenopausal women			
Soyfood intake (g/day)						
T1[d]	160/190	1.00	Referent	51/49	1.00	Referent
T2	203/188	1.36	(0.99-1.86)	49/47	1.12	(0.49-2.55)
T3	144/188	0.83	(0.59-1.26)	47/49	0.55	(0.22-1.36)
P trend		p=0.122			p=0.135	

[a] Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, body mass index, waist-to-hip ratio, age at menarche, physical activity, parity, age at first live birth, alcohol consumption, menopausal status, and total energy intake.
[b] Tertiles of soyfood intake among all women for the parent study they were <6.1, 6.1-11.7, ≥11.8 and for the present study they were <6.6, 6.6-11.9, ≥12.0.
[c] Tertiles of soy intake among premenopausal women for the parent study they were <5.7, 5.7-11.0, ≥11.1 and for the present study they were <6.5, 6.5-11.4, ≥11.5.
[d] Tertiles of soy intake among postmenopausal women for the parent study they were <6.6, 6.6-12.4, ≥12.5 and for the present study they were <7.3, 7.3-12.3, ≥12.4.

Table 3. Odds ratios of breast cancer associated with tertiles of IGF-I levels in the present study, for all women and by menopausal status

	Cases	Controls	OR[a]	(95% CI)
		All women		
IGF-I levels (ng/ml)				
<117.7	106	133	1.00	Referent
117.7-168.4	120	132	1.42	(0.92-2.20)
≥168.4	171	132	2.24	(1.40-3.60)
P trend			p<0.001	
		Premenopausal women		
IGF-I levels (ng/ml)				
<135.9	58	84	1.00	Referent
135.9-181.5	77	83	1.34	(0.72-2.44)
≥181.5	115	85	2.30	(1.28-4.13)
P trend			p=0.001	
		Postmenopausal women		
IGF-I levels (ng/ml)				
<96.4	46	49	1.00	Referent
96.4-130.2	39	47	1.05	(0.43-2.56)
≥130.2	62	49	3.03	(1.18-7.75)
P trend			p=0.021	

[a] Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, body mass index, waist-to-hip ratio, age at menarche, physical activity, parity, age at first live birth, alcohol consumption, menopausal status, and total energy intake.

Table 4. Odds ratios of breast cancer associated with joint effects of medians of soyfood intake and median IGF-I levels, for all women and by menopausal status

	< Median			≥ Median		
	Case/Ctrl	OR[a]	(95% CI)	Case/Ctrl	OR[a]	(95% CI)
			All women			
			Soyfood intake (median=9.2)			
IGF-I levels						
<141.0	79/95	1.00	Referent	82/103	0.89	(0.56-1.44)
≥141.0	117/104	1.54	(0.94-2.52)	119/95	1.70	(1.02-2.83)
			Premenopausal women			
			Soyfood intake (median=8.9)			
IGF-I levels						
<162.1	53/68	1.00	Referent	51/58	1.28	(0.65-2.49)
≥162.1	64/58	1.53	(0.80-2.92)	82/68	2.15	(1.11-4.15)
			Postmenopausal women			
			Soyfood intake (median=9.8)			
IGF-I levels						
<108.7	33/35	1.00	Referent	29/37	0.91	(0.32-2.56)
≥108.7	45/38	2.62	(0.95-7.20)	40/35	1.47	(0.56-3.83)

[a] Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, body mass index, waist-to-hip ratio, age at menarche, physical activity, parity, age at first live birth, alcohol consumption, menopausal status, and total energy intake.

Appendix G

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Letter to the Editor

Reply 1: An assessment of the preconceptional mitochondrial hypothesis

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Abstract

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Reply 1: An assessment of the preconceptional mitochondrial hypothesis

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Sir,

We found Dr van Noord's preconceptional mitochondrial hypothesis interesting particularly in line with a recent report linking polymorphisms of two DNA base excision repair genes (XRCC1 and hOGG1) to breast cancer risk in daughters born to older mothers (Hodgson *et al*, 2003). Manganese superoxide dismutase (MnSOD) may impair the mitochondria's ability to reduce oxidative stress (Oberley and Oberley, 1997). MnSOD has been linked to breast cancer (Ambrosone *et al*, 1999), and may be another pathway through which older maternal age may function. Further support for this hypothesis comes from a recent study that found mitochondrial DNA damage in breast cancer tissue (Richard *et al*, 2000).

To test this hypothesis, we analysed the association of parental age with breast cancer risk using data from the Shanghai Breast Cancer Study (SBCS), and the results are in shown Table 1. After adjustment for established breast cancer risk factors and pregnancy order, we did not find an association between older maternal or paternal age and premenopausal breast cancer in our low-risk population. Additional adjustment for paternal age resulted in a nonsignificantly elevated risk of breast cancer associated with older maternal age. All perinatal information was based on maternal report.

Although we collected information on whether the mother had a threatened miscarriage with the index pregnancy, too few women reported this adverse event (six case mothers, 13 control mothers) to provide a stable risk estimate. Other studies may have sufficient numbers of mothers to investigate this aspect of Dr van Noord's hypothesis.

Dr van Noord argued that insulin-like growth factor- I (IGF-1) might be unlikely to explain the inconsistent findings on birth weight and breast cancer risk in the literature, since the link between IGF-I and breast cancer risk has been found primarily in premenopausal women, while the high birth weight-breast cancer association has been seen among pre- and postmenopausal women. A previous report from the SBCS showed that elevated levels of IGF-I were associated with an increased risk of breast

Table 1 Odds ratios of breast cancer associated with maternal age and paternal age

	Cases ($n=288$)	Controls ($n=350$)	OR[a]	(95% CI)	OR[b]	(95% CI)
Maternal age (years)						
<25	73	98	1.0	(referent)	1.0	(referent)
25–29	123	127	1.4	(0.8–2.3)	1.6	(0.9–2.7)
30–34	63	77	1.1	(0.6–2.0)	1.5	(0.8–2.9)
⩾35	29	47	1.1	(0.5–2.2)	1.6	(0.7–3.9)
P trend			$P=0.84$		$P=0.34$	
Paternal age (years)						
<25	34	41	1.0	(referent)	1.0	(referent)
25–29	96	94	1.4	(0.7–2.8)	1.3	(0.6–2.7)
30–34	88	103	1.3	(0.7–2.7)	1.2	(0.6–2.6)
⩾35	70	111	0.9	(0.4–1.9)	0.7	(0.3–1.8)
P trend			$P=0.13$		$P=0.08$	

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth, and pregnancy order. [b]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, age at first live birth, pregnancy order, and maternal age or paternal age.

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cancer among all women, but the association was more pronounced among women diagnosed premenopausally and among women with a high body mass index or waist-to-hip ratio (Yu *et al*, 2001). We found in a large US study that high birth weight was associated with an elevated risk among premenopausal women (OR = 1.7, 95% CI 1.1–2.5), but a nonsignificantly reduced risk among postmenopausal women (OR = 0.6, 95% CI 0.3–1.1) (Sanderson *et al*, 1996). Therefore, IGF-I as a potential explanation for the birth weight-breast cancer relationship cannot be ruled out.

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